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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/029,579	05/06/98	LANDEGREN U	1209-122P

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EXAMINER	
SHUMAN, J	
ART UNIT	**PAPER NUMBER**
1636	9

DATE MAILED: 08/05/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 09/029,579	Applicant(s) Landegren
	Examiner Jon Shuman	Group Art Unit 1636

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-7* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5 and 7* is/are rejected.

☒ Claim(s) *6* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Claim 6 is objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 2, 3, 4, and 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim "a pharmaceutical composition for targeting double stranded nucleic acids, comprising an effective amount of a padlock probe oligonucleotide having two free nucleic acid end parts which are at least partially complementary to and capable of hybridizing with two at least substantially neighboring respective regions of a target nucleic acid sequence so that the padlock probe can be circularized by joining said free end parts and catenate with the target sequence for direct inhibition thereof." The art in this case involves use of oligonucleotides as pharmaceutical agents. Although the cited art refers to antisense oligonucleotides, the issue is

directed towards the use of oligonucleotides, whether directed towards a sense or an antisense strand, as a pharmaceutical agent. Thus, the issues become irreproducibility of results when using oligonucleotides, for example, in cellular uptake or in unanticipated nonspecific effects and in attempts to translate results obtained by *in vitro* experimentation to *in vivo* models.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with the information known in the art without undue experimentation (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. *In Ex parte Forman,*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in *In re Wands*, 8 USPWQ2d 1400 (Fed. Cir. 1988), the court described the standard of undue experimentation as a standard of reasonableness and set forth the various factors to be considered in the determination of enablement for a claimed invention. These Factors include the following:

1) Unpredictability of the art. The antigene and antisense therapy arts, at the time the invention was made were extremely unpredictable. The activity of oligonucleotides as pharmaceutical agents is unpredictable with regard to nonspecific binding effects on other targets and with regards to non-reproducibility of results *in vivo* and *in vitro*. The pharmacokinetic behavior of oligonucleotide compositions was not predictable even in consideration of *in vitro* test data using model cell lines (Nature Biotechnology 15, 519-528, 1997, see whole article, in particular, p522

column 1 the first paragraph; Antisense Research and Development 4, p67-69, 1994; Science 170, p575-577, 1995; TIBS 23, p45-50, 1998).

2) State of the Art. The antigene and antisense therapy arts at the time of applicant's invention were poorly developed. As noted by Ryszard Cole (Nature Biotechnology 15, 519-528, 1997) "Why is there such a gap between the ability of cultured cells and animal cells to uptake oligos? I am really curious about the mechanisms that are responsible for that" (p521, the article cited). Stanley Crooke adds "I think spending a lot of time trying to understand the differences in what is an interesting topic, but it is a basic research problem that will consume decades of work." (Op. Cit. p522)

3) Number of working examples. The applicants present no working examples of the claimed invention as a treatment or therapeutic agent.

4) Amount of guidance presented by applicants. The only guidance presented by applicants regards *in vitro* biochemistry/enzymology wherein they show the oligonucleotide preparation targets appropriately and inhibits the function of two polymerases in a completely defined test tube reaction. No guidance is provided with regards to using the composition pharmaceutically.

5) Scope of the claims. The broadest claim reads on a pharmaceutical composition for intervention in any disease wherein blocking replication or transcription of a target sequence would have a desired effect. This reads on viral diseases and cancers caused by gene over or mis expression. Thus, the scope of the claimed invention must be considered to be quite broad.

6) Nature of the invention. The invention involves a most complex, most unpredictable area of molecular medicine, the use of oligonucleotides for the treatment of human pathologies.

7) Level of skill in the art. The level of skill in the antigene and antisense therapies is high. However, those of preeminent skill in the art (Op. Cit. Above)face considerable hurdles to successful practicing and use of oligonucleotides as practical pharmaceutical agents (see above) and applicants have not provided teachings sufficient to enable the skilled artisan to overcome said hurdles without having to practice undue and excessive experimentation.

Given the above analysis of the factors which the courts have indicated are critical in determining whether a given invention is enabled, it must be considered that the skilled artisan would have had to have practiced undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Nilsson et al. (Science 265, p2085-2088 1994).

Both applicants and Nilsson et al. (Science 265, p2085-2088 1994 see whole document) recite the same "composition for targeting nucleic acids, comprising a padlock probe having two free nucleic acid end parts which are partially complementary to and hybridize with two neighboring regions of a target nucleic acid sequence so that it can be circularized and catenate with the target

sequence." An intended use claim for a composition is given no patentable weight. Therefore, Nilsson et al teaches the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5, and 7 are rejected under 35 U.S.C. 112, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague in the recitation of the phrase "characterized in that", which is not further limiting in its meaning. Replacing the phrase "characterized in that" with the term wherein constitutes usage in compliance with 35 U.S.C. 112 (second paragraph).

Claims 1 and 7 are vague in the recitation of the phrase "an effective amount", which is not further defined by the claim, that is, effective to do what? Claim 1 is directed to "direct inhibition thereof", which does not clearly define an objective, thus it is unclear if applicants seek to inhibit transcription, or what? The term effective amount is left undefined.

3. Claims 1 and 7 are vague in the recitation of the phrases "are at least partially complementary to and capable of hybridizing with" and "with two at least substantially neighboring respective regions" which are relative terms that render the claim indefinite. The terms "are at least partially complementary to and capable of hybridizing with" and "with two at

least substantially neighboring respective regions" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The phrases might be replaced with " hybridize" and "with two closely apposed sequences".

Claim 7 is vague in that it recites an intended use for a claimed composition. Intended use language in a composition claim carries no patentable weight and is improper claim language.

4. Claim 3 is vague in the recitation of the phrase "linking agent". In the independent claim, claim 1, reference is made to "joining said free nucleic acid end parts". In the instant claim, it is not clear what is being linked.

Claim 4 is objected to for the phrase "wherein linking agent. The claim should read "wherein said linking agent.

McShan et al (J. Biol. Chem. 267 (8) p5712-21 1992) and Giovannangeli et al. (Proc. Natl. Acad. Sci 90 p10013-17 1993) are cited as of interest.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Shuman whose telephone number is (703) 306-5819. The examiner can normally be reached on Monday to Friday from 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon Shuman

07/30/99

DAVID GUZO
PRIMARY EXAMINER